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1.	Your Reference	RMT/PB60299P 0319124.4
2.	Patent application number *(The Patent office will fill in this part)*	14 AUG 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**SMITHKLINE BEECHAM CORPORATION** **ONE FRANKLIN PLAZA** **P.O. BOX 7929** **PHILADELPHIA** **PENNSYLVANIA 19101** **UNITED STATES OF AMERICA**
	Patents ADP number *(if you know it)*	59494170004
	If the applicant is a corporate body, give the country/state of its corporation	**UNITED STATES OF AMERICA**
4	Title of the invention	**CHEMICAL COMPOUNDS**
5	Name of your agent *(if you know one)*	**RACHEL M THORNLEY**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**GLAXOSMITHKLINE** **CORPORATE INTELLECTUAL PROPERTY (CN9 25.1)** **980 GREAT WEST ROAD** **BRENTFORD, MIDDLESEX** **TW8 9GS, GB**
	Patents ADP number *(if you know it)*	8072555 00

		Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)
6.	If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

		Number of earlier application	Date of filing (day / month / year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8.	Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	**YES**

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Continuation sheets of this form	-
Description	27
Claim(s)	8
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10. If you are also filing any of the following, state how many against each item

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Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature ***RACHEL M THORNLEY*** **14 August, 2003**
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JACKIE ROBINSON

020 8047 4458

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CHEMICAL COMPOUNDS

The present invention relates to therapeutically active compounds which are anthranilic acid derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, particularly in the treatment of diseaseswhere under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial.

Dyslipidaemia is a general term used to describe individuals with aberrant lipoprotein profiles. Clinically, the main classes of compounds used for the treatment of patients with dyslipidaemia, and therefore at risk of cardiovascular disease are the statins, fibrates, bile-acid binding resins and nicotinic acid. Nicotinic acid (Niacin, a B vitamin) has been used clinically for over 40 years in patients with various forms of dyslipidaemia. The primary mode of action of nicotinic acid is via inhibition of hormone-sensitive triglyceride lipase (HSL), which results in a lowering of plasma non-esterified fatty acids (NEFA) which in turn alters hepatic fat metabolism to reduce the output of LDL and VLDL (low and very low density lipoprotein). Reduced VLDL levels are thought to lower cholesterol ester transfer protein (CETP) activity to result in increased HDL (high density lipoprotein) levels which may be the cause of the observed cardiovascular benefits. Thus, nicotinic acid produces a very desirable alteration in lipoprotein profiles; reducing levels of VLDL and LDL whilst increasing HDL. Nicotinic acid has also been demonstrated to have disease modifying benefits, reducing the progression and increasing the regression of atherosclerotic lesions and reducing the number of cardiovascular events in several trials.

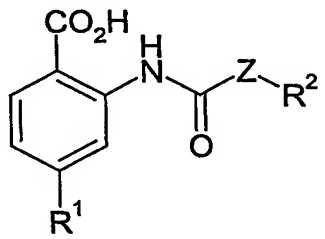
The observed inhibition of HSL by nicotinic acid treatment is mediated by a decrease in cellular cyclic adenosine monophosphate (cAMP) caused by the G-protein-mediated inhibition of adenylyl cyclase. Recently, the G-protein coupled receptors HM74 and HM74A have been identified as receptors for nicotinic acid (PCT patent application WO02/84298; Wise et. al. J Biol Chem. 2003 **278** (11) 9869-9874). Two other papers support this discovery, (Tunaru et. al. Nature Medicine 2003 (3) 352-255 and Soga et. al. Biochem Biophys Res Commun. 2003 **303** (1) 364-369), however the nomenclature differs slightly. In the Tunaru paper what they term human HM74 is in fact HM74A and in the Soga paper HM74b is identical to HM74A. Cells transfected to express HM74A and/or HM74 gain the ability to elicit G_i G-protein mediated responses following exposure to nicotinic acid. In mice lacking the homologue of HM74A (m-PUMA-G) nicotinic acid fails to reduce plasma NEFA levels.

Certain anthranilic acid derivatives have been synthesised and disclosed in the prior art; some of these compounds have been shown to have utility in therapy, as outlined below.

Intermediates, formulations, methods and processes described herein form further aspects of the invention.

Detailed Description of the Invention

The present invention provides a compound of Formula (I)



(I)

and salts, solvates and physiologically functional derivatives thereof, wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

Z represents $-(CH_2)_n-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_nO-$; $-C(R^4R^5)O-$ or $-Y-W-X-$;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 or 2;

q represents an integer selected from 1, 2, 3 and 4;

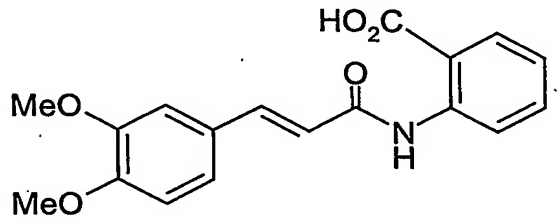
R^3 represents hydrogen or methyl; and

R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl;

provided

(i) that when R^1 is hydrogen, Z is $-(CH_2)_n-$, and n is 2, then R^2 is other than para-chlorophenyl or para-methylphenyl;

(ii) that a compound of Formula (I) is other than 2-(2-(((4-(phenyl)phenyl) amino)acetyl)amino)benzoic acid, 2-(2-(((4-phenyl)phenoxy)acetyl)amino) benzoic acid, 2-[[(4-cyclohexylphenoxy)acetyl]amino]benzoic acid, 2-[[3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-1-oxopropyl]amino]benzoic acid or compound X



X.

The R^2 ring system may be joined to the Z linker unit via either a ring carbon atom or via a ring heteroatom, where present.

Preferred R^1 groups are hydrogen or C_1-C_3alkyl, for example hydrogen or methyl, especially hydrogen.

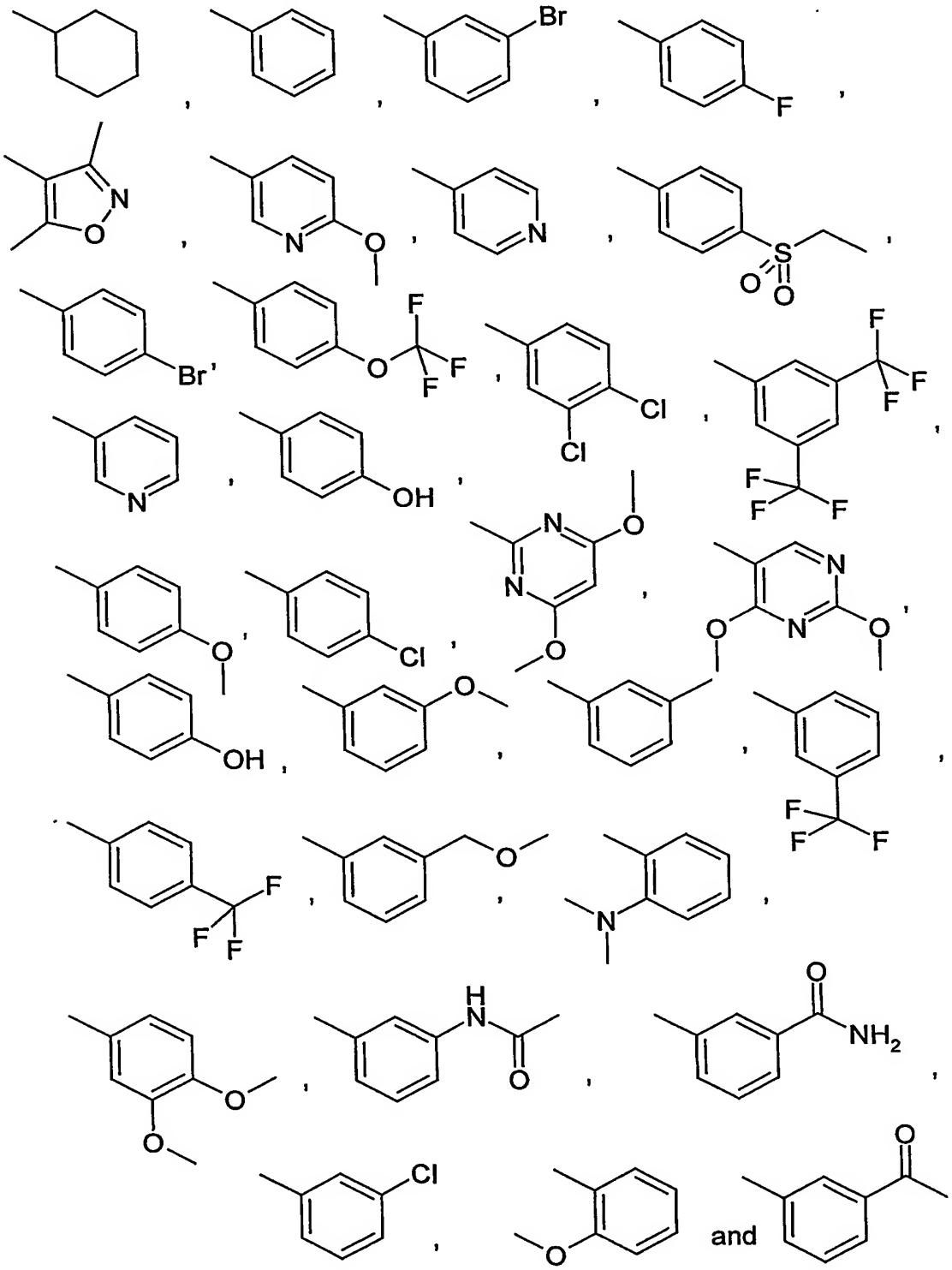
Preferred R^2 heteroaryl groups include pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrazolyl, imidazolyl, oxazolyl and isoxazolyl. Preferred R^2 heterocyclic groups include pyrrolidinyl, imidazolidinyl, piperidinyl and morpholinyl.

Thus, preferred R^2 groups include cyclohexyl, phenyl, pyridinyl, pyrimidinyl, pyridazinyl and isoxazolyl, with phenyl being particularly preferred. Further prefered R^2 groups include substituted cyclohexyl, substituted phenyl, substituted pyridine, substituted pyrimidine, substituted pyridazine or substituted isoxazole, in which the substituents are as defined further below, with substituted phenyl being particularly preferred.

Thus, where R^2 is substituted phenyl, the substituents will be those defined for "aryl" substituents below. However, in prefered embodiments the substituted phenyl bears one or two substituents selected from halogen C_{1-3}alkyl, C_{1-3}haloalkyl C_{1-3}alkoxy and C_{1-3}haloakloxy. Particularly prefered C_{1-3}haloalkyl and C_{1-3}haloakloxy substituents on an R^2 phenyl group are trifluoro groups, such as trifluoromethylphenyl or trifluoromethoxyphenyl, whilst particularly prefered R^2 phenyl C_{1-3}alkyl and C_{1-3}alkoxy substituents are methylphenyl and methoxyphenyl, respectively.

In singly substituted phenyl at R^2, the substituent is preferably at the meta or para position, desirably para. Double substitution preferably occurs at the para and meta, or at both meta positions.

In certain preferred embodiments, R^2 is selected from the group consisting of:



and

Z preferably represents –Y-W-X–, $-(CH_2)_n-$, $-(CH_2)_pO-$ or $-(CH_2)_pNHC(O)-$.

Y preferably represents –O– or $-CH_2-$. X is preferably absent or represents $-(CH_2)_pSO_2NR^3-$, $-(CH_2)_pNHC(O)-$ or $-(CH_2)_pNHC(O)NH-$. When Y represents $-CH_2-$, X preferably represents $-(CH_2)_pSO_2NR^3-$. When Y represents –O–, X is preferably absent.

Preferred W groups are 5 or 6 member aryl or heteroaryl rings. Where W is aryl, a 6 member ring is prefered, especially phenyl (preferably linked through the 1 and 4 or the 1 and 3 positions), whilst where W is heteroaryl a 5 member ring is particularly prefered, especially 1, 2, 4 oxadiazole (preferably linked through the 3 and 5 positions). Unsubstituted phenyl is particularly prefered. When X is $-(CH_2)_pSO_2NR^3-$, p is 0 and W is unsubstituted phenyl, W is desirably linked through the 1 and 4 (para) positions.

In certain prefered embodiments, n represents 2.

In certain prefered embodiments, p represents an integer selected from 0 or 1.

In certain prefered embodiments W and R^2 each represent unsubstituted phenyl, whilst in other prefered embodiments W represents unsubstituted phenyl and R^2 represents substituted phenyl.

It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above.

Throughout the present specification and the accompanying claims the words "comprise" and "include" and variations such as "comprises", "comprising", "includes" and "including" are to be interpreted inclusively. That is, these words are intended to convey the possible inclusion of other elements or integers not specifically recited, where the context allows

As used herein, the terms "halogen" or "halo" refer to fluorine, chlorine, bromine and iodine.

As used herein, the term "alkyl" (when used as a group or as part of a group) refers to an optionally substituted straight or branched hydrocarbon chain containing the specified number of carbon atoms. For example, C_1-C_3alkyl means a straight or branched hydrocarbon chain containing at least 1 and at most 3 carbon atoms. Examples of alkyl as used herein include, but are not limited to; methyl (Me), ethyl

(Et), n-propyl, i-propyl and the like. Unless otherwise stated, optional substituents include hydroxy, halogen, =S and =O.

As used herein, the term "alkoxy" (when used as a group or as part of a group) refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Examples of alkoxy as used herein include, but are not limited to; methoxy, ethoxy, n-propoxy, i-propoxy and the like.

As used herein, the term "alicyclic" (when used as a group or as part of a group) refers to a cyclic hydrocarbon ring containing the specified number of carbon atoms. Examples of alicyclic as used herein include, but are not limited to cyclohexyl, cyclopropyl and the like. Said alicyclic groups may be optionally substituted with one or more, for example 1 to 3, groups selected from hydroxy, halogen, =S, =O, C_1-C_3alkyl (which may be further substituted with one or more hydroxy, =O or halo groups), optionally halogenated C_1-C_3alkoxy, C_1-C_3alkoxyC_1-C_3alkyl, NR^3_2, -$NHC(O)C_1$-C_3alkyl, -$C(O)NR^3_2$, and -$S(O)_2C_1$-C_3alkyl, wherein R^3 is as defined above.

As used herein, the term "aryl" (when used as a group or as part of a group) refers to an aromatic hydrocarbon ring of the specified number of carbons. Examples of aryl as used herein include, but are not limited to, phenyl and benzyl. Said aryl groups may be optionally substituted with one or more, for example 1 to 3 groups selected from hydroxy, halogen, =S, =O, C_1-C_3alkyl (which may be further substituted with one or more hydroxy, =O or halo groups), optionally halogenated C_1-C_3alkoxy, C_1-C_3alkoxyC_1-C_3alkyl, NR^3_2, -$NHC(O)C_1$-C_3alkyl, -$C(O)NR^3_2$, and -$S(O)_2C_1$-C_3alkyl, wherein R^3 is as defined above.

As used herein, the term "heteroaryl" (when used as a group or as part of a group) refers to an aryl group, as defined above, which contains one or more nitrogen or oxygen heteroatoms. Examples of heteroaryl as used herein include, but are not limited to, pyridine, pyrimidine, pyridazine, imidazole, isoxazole, oxadiazoles and the like. Said heteroaryl groups may be optionally substituted with one or more, for example 1 to 3 groups selected from hydroxy, halogen, =S, =O, C_1-C_3alkyl (which may be further substituted with one or more hydroxy, =O or halo groups), optionally halogenated C_1-C_3alkoxy, C_1-C_3alkoxyC_1-C_3alkyl, NR^3_2, -$NHC(O)C_1$-C_3alkyl, -$C(O)NR^3_2$, and -$S(O)_2C_1$-C_3alkyl, wherein R^3 is as defined above.

As used herein, the term "heterocyclic" (when used as a group or as part of a group) refers to an alicyclic group, as defined above, which contains one or more nitrogen or oxygen heteroatoms. Said heterocyclic groups may be optionally substituted with one or more, for example 1 to 3 groups selected from hydroxy, halogen, =S, =O, C_1-C_3alkyl (which may be further substituted with one or more hydroxy, =O or halo

groups), optionally halogenated C_1-C_3alkoxy, C_1-C_3alkoxyC_1-C_3alkyl, NR^3_2, -$NHC(O)C_1$-C_3alkyl, -$C(O)NR^3_2$, and -$S(O)_2C_1$-C_3alkyl, wherein R^3 is as defined above.

As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example an ester or an amide thereof, and includes any pharmaceutically acceptable salt, ester, or salt of such ester of a compound of Formula (I) which, upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) a compound of Formula (I) or an active metabolite or residue thereof. It will be appreciated by those skilled in the art that the compounds of Formula (I) may be modified to provide physiologically functional derivatives thereof at any of the functional groups in the compounds, and that the compounds of Formula (I) may be so modified at more than one position.

As used herein, the term "pharmaceutically acceptable" used in relation to an ingredient (active ingredient or excipient) which may be included in a pharmaceutical formulation for administration to a patient, refers to that ingredient being acceptable in the sense of being compatible with any other ingredients present in the pharmaceutical formulation and not being deleterious to the recipient thereof.

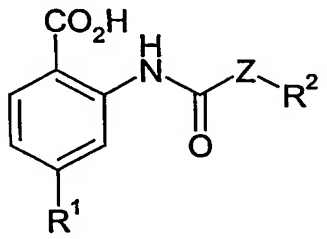
As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (I), a salt thereof or a physiologically functional derivative thereof) and a solvent. Such solvents for the purposes of the present invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water, in which case the solvate may be referred to as a hydrate of the solute in question.

It will be appreciated that, for pharmaceutical use, the "salt or solvate" referred to above will be a pharmaceutically acceptable salt or solvate. However, other salts or solvates may find use, for example, in the preparation of a compound of Formula (I) or in the preparation of a pharmaceutically acceptable salt or solvate thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Suitable pharmaceutically acceptable salts include acid addition salts formed from the addition of inorganic acids or organic acids, preferably inorganic acids. Examples of suitable acid addition salts include hydrochlorides, hydrobromides, sulphates and acetates. Further representative examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic,

ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids. Suitable pharmaceutically acceptable salts also include alkali metal salts formed from the addition of alkali metal bases such as alkali metal hydroxides. An example of a suitable alkali metal salt is a sodium salt.

In a further aspect, the present invention provides the use of a compound of Formula (Ia)



(Ia)

and salts, solvates and physiologically functional derivatives thereof in the manufacture of a medicament for the treatment of disorders of lipid metabolism, including dislipidaemia or hyperlipoproteinaemia, or of inflammatory diseases or conditions

wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, or heterocyclic or alicyclic ring;

Z represents $-(CH_2)_n-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_qO-$; $-C(R^4R^5)O-$ or $-Y-W-X-$;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 or 2;

q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl.

It is to be understood that this aspect of the present invention relates with respect to the use of compounds of Formula (Ia), to all combinations of particular and preferred groups described herein above for compounds of Formula (I).

Compounds of the present invention are of potential therapeutic benefit in the treatment and amelioration of the symptoms of many diseases of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke. The use of a compound of Formula (Ia) in the treatment of one or more of these diseases is a further aspect of the present invention.

Furthermore, it is also believed that the HM74 and HM74A receptors are involved in inflammation. Inflammation represents a group of vascular, cellular and neurological responses to trauma. Inflammation can be characterised as the movement of inflammatory cells such as monocytes, neutrophils and granulocytes into the tissues. This is usually associated with reduced endothelial barrier function and oedema into the tissues. Inflammation with regards to disease typically is referred to as chronic inflammation and can last up to a lifetime. Such chronic inflammation may manifest itself through disease symptoms. The aim of anti-inflammatory therapy is therefore to reduce this chronic inflammation and allow for the physiological process of healing and tissue repair to progress.

Thus, a further aspect of the present invention resides in the use of a compound of Formula (Ia) or a salt, solvate or physiologically functional derivative thereof in the treatment of inflammatory diseases or conditions of the joint, particularly arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes melitus and complications thereof, of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well

as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosis, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

In particular, the compounds of Formula (Ia) are useful in the treatment and prevention of inflammation, diabetes and cardiovascular diseases or conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and mixed dyslipidaemia.

Thus, there is also provided the use of a compound of Formula (Ia) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds are also provided for use in the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

Nicotinic acid has a significant side effect profile, possibly because it is dosed at high level (gram quantities daily). The most common side effect is an intense cutaneous flushing. The compounds of the present invention preferably exhibit reduced side effects compared to nicotinic acid.

HM74A has been identified as a high affinity receptor for nicotinic acid whilst HM74 is a lower affinity receptor. The compounds of the present invention are selective for HM74A. Thus, they show greater affinity for HM74A than for HM74.

The potential for compounds of Formula (I) to activate HM74A may be demonstrated, for example, using the following *in vitro* and *in vivo* assays:

<u>In-vitro testing</u>

For transient transfections, HEK293T cells (HEK293 cells stably expressing the SV40 large T-antigen) were maintained in DMEM containing 10 % foetal calf serum and 2 mM glutamine. Cells were seeded in 90 mm culture dishes and grown to 60-80 % confluence (18-24 h) prior to transfection with vectors containing the relevant DNA inserts using Lipofectamine reagent. For transfection, 9 μg of DNA was mixed with 30 μl Lipofectamine in 0.6 ml of Opti-MEM (Life Technologies Inc.) and was incubated at room temperature for 30 min prior to the addition of 1.6 ml of Opti-MEM. Cells were

exposed to the Lipofectamine/DNA mixture for 5 h and 6 ml of 20 % (v/v) foetal calf serum in DMEM was then added. Cells were harvested 48 h after transfection. Pertussis toxin treatment was carried out by supplementation into media at 50 $ngml^{-1}$ for 16 h. All transient transfection studies involved co-transfection of receptor together with the $G_{i/o}$ G protein, $G_{o1}\alpha$.

For generation of stable cell lines the above method was used to transfect CHO-K1 cells seeded in six well dishes grown to 30 % confluence. These cells were maintained in DMEM F-12 HAM media containing 10 % foetal calf serum and 2 mM glutamine. 48 h post-transfection the media was supplemented with 400μg/ml G418 for selection of antibiotic resistant cells. Clonal CHO-K1 cell lines stably expressing HM74A were confirmed by [^{35}S]-GTPγS binding measurements, following the addition of nicotinic acid.

P2 membrane preparation - Plasma membrane-containing P2 particulate fractions were prepared from cell pastes frozen at –80°C after harvest. All procedures were carried out at 4°C. Cell pellets were resuspended in 1 ml of 10 mM Tris-HCl and 0.1 mM EDTA, pH 7.5 (buffer A) and by homogenisation for 20 s with a Ultra Turrax followed by passage (5 times) through a 25-gauge needle. Cell lysates were centrifuged at 1,000 *g* for 10 min in a microcentrifuge to pellet the nuclei and unbroken cells and P2 particulate fractions were recovered by microcentrifugation at 16,000 *g* for 30 min. P2 particulate fractions were resuspended in buffer A and stored at –80°C until required.

[^{35}S]-GTPγS binding - assays were performed at room temperature in 96-well format as described previously (Wieland, T. and Jakobs, K.H. (1994) *Methods Enzymol.* **237,** 3-13). Briefly, membranes (10 μg per point) were diluted to 0.083 mg/ml in assay buffer (20 mM HEPES, 100 mM NaCl, 10 mM $MgCl_2$, pH7.4) supplemented with saponin (10 mg/l) and pre-incubated with 10 μM GDP. Various concentrations of nicotinic acid or related molecules were added, followed by [^{35}S]-GTPγS (1170 Ci/mmol, Amersham) at 0.3 nM (total vol. of 100 μl) and binding was allowed to proceed at room temperature for 30 min. Non-specific binding was determined by the inclusion of 0.6 mM GTP. Wheatgerm agglutinin SPA beads (Amersham) (0.5 mg) in 25μl assay buffer were added and the whole was incubated at room temperature for 30 min with agitation. Plates were centrifuged at 1500 g for 5 min and bound [^{35}S]-GTPγS was determined by scintillation counting on a Wallac 1450 microbeta Trilux scintillation counter.

Compounds according to Formula (I) have been synthesised (see synthetic examples below)and tested in the assays discussed above. All of the compounds have an EC50 of 5.0 or greater and an efficacy of 30% or greater.

In-vivo testing

HM74A agonists are tested in male Spague-Dawley rats (200-250grammes) which have been fasted for at least 12 hours prior to the study. The compounds are dosed intravenously (5ml/kg) or by oral gavage (10ml/kg). Blood samples (0.3ml tail vein bleed) are taken pre-dose and at three times post-dose (times ranging from 15minutes to 8 hours post-dose). Each blood sample is transferred to a heparin tube (Becton Dickinson Microtainer, PST LH) and centrifuged (10,000 *g* for 5 minutes) to produce a plasma sample. The plasma samples are assayed for levels of non-esterified fatty acids (NEFA) using a commercially available kit (Randox). Inhibition of plasma NEFA levels, relative to pre-dose levels, is used as a surrogate for HM74A agonist activity.

As indicated above, compounds of Formula (I) are useful in human or veterinary medicine, in particular as activators of HM74A, in the management of dyslipidaemia and hyperlipoproteinaemia.

Thus, there is provided as a further aspect of the present invention a compound of Formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, for use in human or veterinary medicine, particularly in the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds are also provided for use in the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

It will be appreciated that references herein to treatment extend to prophylaxis, prevention of recurrence and suppression of symptoms as well as the treatment of established conditions.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with a where under-activation of the HM74A receptor contributes to the condition or where activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of a compound of Formula (I) or a physiologically acceptable salt or solvate thereof.

More particularly, the present invention provides a method for the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and

hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, which method comprises administering to said human or animal subject an effective amount of a compound of Formula (Ia) or a physiologically acceptable salt or solvate thereof. As such, these compounds may also find favour in methods for the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, which methods comprise administering to said human or animal subject an effective amount of a compound of Formula (I) or a physiologically acceptable salt, solvate or derivative thereof.

The amount of a HM74A modulator which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the mode of administration and the precise clinical condition of the recipient. In general, the daily dose will be in the range of 0.1mg - 1g/kg, typically 0.1 - 100mg/kg. An intravenous dose may, for example, be in the range of 0.01mg to 0.1g/kg, typically 0.01mg to 10mg/kg, which may conveniently be administered as an infusion of from 0.1μg to 1mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01μg to 0.1mg, per millilitre. Unit doses may contain, for example, from 0.01μg to 1g of a HM74A modulator. Thus ampoules for injection may contain, for example, from 0.01μg to 0.1g and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1mg to 1g. No toxicological effects are indicated/expected when a compound of the invention is administered in the above mentioned dosage range.

A compound of the present invention may be employed as the compound *per se* in the treatment of a the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficia, but is preferably presented with an acceptable carrier in the form of a pharmaceutical formulation. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the HM74A modulator as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the HM74A modulator.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration.

There is also provided according to the invention a process for preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges or tablets, each containing a predetermined amount of a HM74A modulator; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. In general, the formulations are prepared by uniformly and intimately admixing the active HM74A modulator with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or moulding a powder or granules of the HM74A modulator optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a HM74A modulator in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the HM74A modulator in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of an HM74A modulator, preferably isotonic with the blood of the intended recipient. These preparations are

preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the HM74A modulator with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the HM74A modulator.

Thus, formulations of the present invention suitable for parenteral administration comprising a compound according to the invention may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or toxicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

Formulations suitable for rectal administration are preferably presented as unit-dose suppositories. These may be prepared by admixing a HM74A modulator with one or more conventional solid carriers, for example, cocoa butter or glycerides and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The HM74A modulator is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2- tetrafluorethane, carbon dioxide or other suitable gas.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatin, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example in combination with other classes of dyslipidaemic drugs (e.g. statins, fibrates, bile-acid binding resins or nicotinic acid).

The compounds of the instant invention may be used in combination with one or more other therapeutic agents for example in combination with other classes of dyslipidaemic drugs e.g. 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) or fibrates or bile acid binding resins or nicotinic acid. The invention thus provides, in a further aspect, the use of such a combination in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial and the use of a compound of Formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof in the manufacture of a medicament for the combination therapy of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa or obesity.

When the compounds of the present invention are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optimally together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When combined in the same formulation it will be appreciated that the two components must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

When in combination with a second therapeutic agent active against the same disease, the dose of each component may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent.

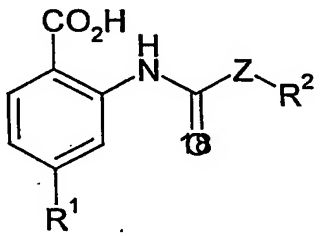
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

The compounds of the Formula (I) have useful duration of action.

Compounds of Formula (I) and salts and solvates thereof may be prepared by various synthetic routes, including the methodology described hereinafter which constitutes a further aspect of the invention.

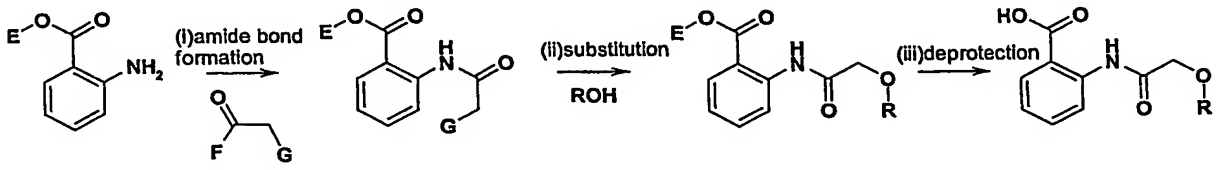
Method A:

A process for preparing a compound of Formula (I)



(I)

in which R^1 represents hydrogen, Z represents -Y-W-X-, Y represents $-(CH_2)_pO-$, p represents the integer 1, and W, X and R^2 are as defined above is set out in scheme (a):



E = protecting group
F = activating group for acyl transfer
G = leaving group
R = W-X-R^2

Scheme (a)

A process according to the invention for preparing a compound of Formula (I) comprises:

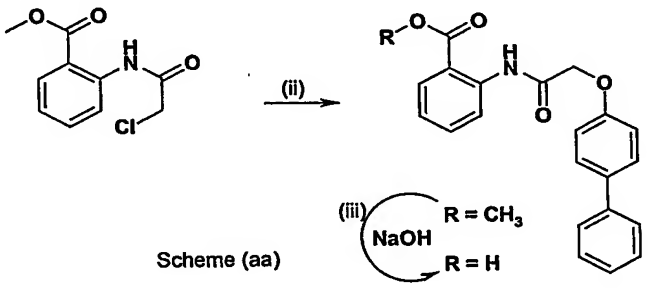
(i) amide bond formation by acetylation of an ester of anthranilic acid;

(ii) addition of W or W-X-R^2 by substitution of G;

(iii) deprotection of the anthranilic acid group;

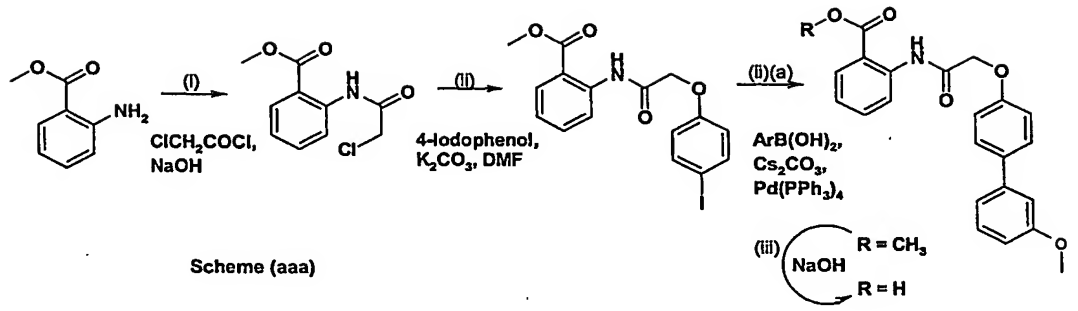
and where desired or necessary converting a resultant free acid or base compound of Formula (I) into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.

A particular example of a process according to Method A is set out in scheme (aa), which illustrates steps (ii) and (iii) of the method:



Scheme (aa)

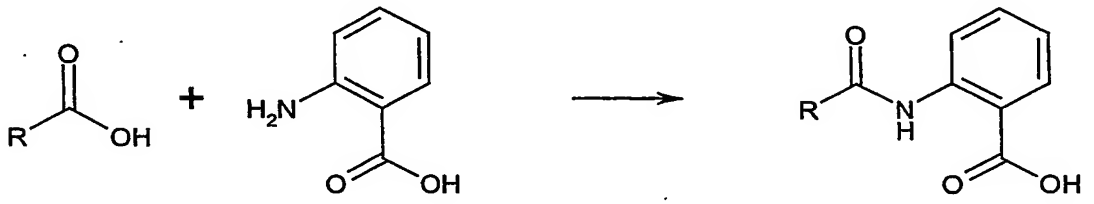
Another particular example of a process according to Method A is set out in scheme (aaa):



Scheme (aaa)

in which step (ii) comprises addition of W and a further step (ii)(a), addition of R^2, is included in the form of a further substitution reaction.

Method B



wherein R represents $-Z-R^2$ as defined above.

A further process according to the invention for preparing a compound of Formula (I) comprises:

(i) formation of an amide between the amine group of anthranilic acid (2-amino-bezoic acid) and an activated acyl transfer reagent derived from a carboxylic acid

(ii) where desired or necessary converting a resultant free acid or base compound of Formula (I) into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.

ABBREVIATIONS

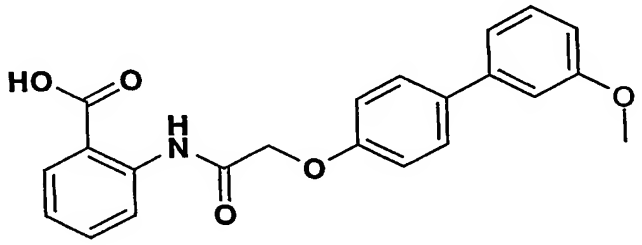
DMSO	Dimethylsulphoxide
DCM	Dichloromethane
THF	Tetrahydrofuran
TFA	Trifluoroacetic Acid
DMF	Dimethylformamide
HBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate

The following non-limiting examples illustrate the present invention:

Synthetic Examples:

A. Example compounds synthesised using Method A, scheme (a) or scheme (aaa)

Example 1: 2-[2-(3'-Methoxy-biphenyl-4-yloxy)-ethanoylamino]-benzoic acid



a) 2-(2-Chloro-ethanoylamino)-benzoic acid methyl ester

Methyl anthranilate (0.85 ml, 6.6 mmole, 1 equiv) and chloroacetyl chloride (0.63 ml, 7.9 mmole, 1.2 equiv) were stirred vigorously in a mixture of THF (10 ml) and water (10 ml) and cooled to 4°C while a 2M solution of NaOH (3.3 ml) was slowly added. After 0.5 hours, the reaction mixture was extracted twice with ethyl acetate and the organic solution was washed with brine, dried with magnesium sulphate and evaporated to dryness. The resulting solid (1.5 g) was triturated with two aliquots of hexane to give the title compound as a white solid (1.15 g, 76%); δ_H (400MHz, $CDCl_3$) 3.96 (3H, s), 4.21 (2H, s), 7.34 (1H, dd, J = 1.2 and 7.6 Hz), 7.58 (1H, dd, J = 1.6 and 7.6 Hz), 8.07 (1H, dd, J = 1.6 and 8 Hz), 8.65 (1H, dd, J = 1.2 and 8.8 Hz); m/z 250.0 [MNa^+].

b) 2-[2-(4-Iodo-phenoxy)-ethanoylamino]-benzoic acid methyl ester ,

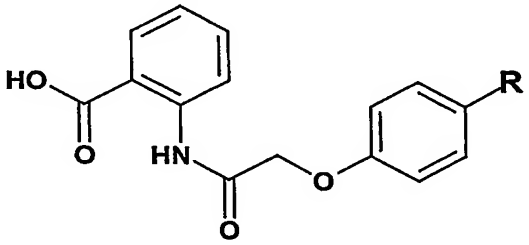
2-(2-Chloro-ethanoylamino)-benzoic acid methyl ester **2** (0.5 g, 2.2 mmole,1 equiv), K_2CO_3 (0.46 g, 3.3 mmole,1.5 equiv), and 4-iodophenol (0.58 g, 2.64 mmole,1.2 equiv) were heated together in DMF (10 ml) at 90°C for 6 hr. The solvent was evaporated and the residue crystallised from t-butylmethyl ether to yield the title compound (480 mg, 53%); δ_H (400MHz, CD_3OD) 3.95 (3H, s), 4.68 (2H, s), 6.94 – 6.98 (2H, m), 7.20 (1H, dt, J = 1.1 and 7.7 Hz), 7.65 (1H, dt, J = 1.7 and 7.3 Hz), 7.63 – 7.67 (2H, m), 8.09 (1H, J = 1.6 and 8.1 Hz), 8.71 (1H, dd, J = 0.9 and 8.4 Hz); m/z 412.0 [MH^+], 434.0 [MNa+].

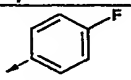
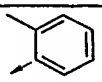
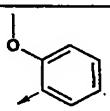
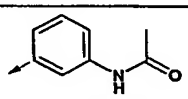
c) 2-[2-(3'-Methoxy-biphenyl-4-yloxy)-ethanoylamino]-benzoic acid,

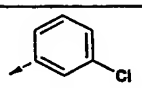
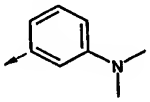
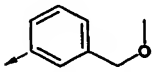
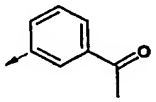
3-Methoxyphenylboronic acid (44.4 mg, 0.29 mmole, 1.2 equiv), Cs_2CO_3 (325 mg, 1 mmole, 4 equiv) and 2-[2-(4-Iodo-phenoxy)ethanoylamino]-benzoic acid methyl ester (100 mg, 0.24 mmole, 1 equiv) were dissolved in THF / water (5/1, 25 ml) and degassed by bubbling a stream of argon through the solution for 25 minutes. Tetrakistriphenylphosphine palladium (5.8 mg, 0.005 mmole, 0.02equiv) was added and the reaction mixture was heated for 18 hours at 80°C under an atmosphere of argon.

The reaction mixture was treated with ethanol (5 ml) and water (5 ml), basified with 2M NaOH and heated to reflux for 4 hours. After cooling, the reaction mixture was acidified with HCl and extracted twice with ethyl acetate. The combined extracts were dried with magnesium sulphate and evaporated to dryness. The crude solid (66 mg) was chromatographed over a column of silica 60 eluting with DCM / MeOH (9 : 1) to give the product 2-[2-(3'-Methoxy-biphenyl-4-yloxy)-ethanoylamino]-benzoic acid as a white solid (44 mgs, 40%); δ_H (400MHz, DMSO-d6) 3.81 (3H, s), 4.75 (2H, s), 6.89 (1H, dd, J = 0.8 and 8 Hz), 7.10-7.20 (5H, m), 7.34 (1H, t, J = 8 Hz), 7.51 (1H, br t), 7.64 (2H, m), 8.03 (1H, dd, J = 1.6 and 8 Hz), 8.65 (1H, d, J = 8 Hz); m/z 378.2 [MH^+].

The following compounds of Examples 2-9 were also prepared using the Method of Example 1:



Example No:	Compound: R =	yield	m/z
2		8 mg 13%	366.1
3		6.7 mg 11%	362.2
4		7.5 mg 12%	378.1
5		2.1 mg 3%	405.1

6		6.1 mg 12%	382.2
7		9.1 mg 14%	391.2
8		4.2 mg 6.6%	392.2
9		4.9 mg 7.7%	390.1

Example 2: δ_H (400MHz, DMSO-d6) 4.78 (2H, s), 7.10 -7.32 (5H, m), 7.55 – 7.73 (5H, m), 8.03 (1H, dd, J = 1.6 and 8.0 Hz), 8.71 (1H, dd, J = 3.7 and 8.4 Hz), 12.13 – 12.29 (1H, m), 13.50 – 13.90 (1H, br s).

Example 3: δ_H (400MHz, CD_3OD) 2.23 (3H, s), 4.72 (2H, s), 7.15-7.30 (9H, m), 7.57 (1H, dd, J = 8 and 1.2 Hz), 8.11 (1H, dd, J = 1.6 and 8 Hz), 8.72 (1H, dd, J = 0.8 and 8.4 Hz).

Example 4: δ_H (400MHz, DMSO-d6) 3.76 (3H, s), 4.78 (2H, s), 7.01 (1H, t, J = 7.4 Hz), 7.08 – 7.14 (3H, m), 7.26 (1H, t, J = 7.3 Hz), 7.27 – 7.36 (2H, m), 7.44 – 7.47 (2H, m), 7.60 – 7.66 (1H, m), 8.03 (1H, dd, J = 1.6 and 8.0 Hz), 8.72 (1H, dd, J = 1.6 and 8.4 Hz),

Example 5: δ_H (400MHz, DMSO-d6) 2.06 (3H, s), 4.78 (2H, s), 7.17 -7.20 (3H, m), 7.25 – 7.30 (1H, m), 7.35 (1H, t, J = 8.0 Hz), 7.50 – 7.53 (1H, m), 7.56 – 7.64 (3H, m), 7.83 – 7.85 (1H,m), 8.02 (1H, d, J = 8 Hz), 8.70 (1H, d, J = 8.0 Hz),

Example 6: δ_H (400MHz, DMSO-d6) 4.80 (2H, s), 7.17 -7.20 (3H, m), 7.37 – 7.41 (1H, m), 7.47 (1H, t, J = 8.0 Hz), 7.56 – 7.75 (5H, m), 8.03 (1H, dd, J = 1.6 and 8.0 Hz), 8.72 (1H, dd, J = 0.8 and 8.4 Hz), 12.25 (1H, s), 13.60 – 14.00 (1H, br s).

Example 7: δ_H (400MHz, DMSO-d6) 2.97 (6H, s), 4.79 (2H, s), 6.74 - 6.77 (1H, m), 6.94 – 7.00 (2H, m), 7.12 – 7.29 (4H, m), 7.62 – 7.67 (3H, m), 8.03 (1H, dd, J = 1.6 and 8 Hz), 8.72 (1H, dd, J = 0.8 and 8.4 Hz), 12.20 (1H, s).

Example 8: δ_H (400MHz, DMSO-d6) 3.32 (3H, s), 4.47 (2H, s), 4.79 (2H, s), 7.16 -7.23 (3H, m), 7.27 (1H, d, J = 7.6 Hz), 7.42 (1H, t, J = 8.0 Hz), 7.54 – 7.56 (2H, m), 7.64 – 7.67 (3H, m), 8.03 (1H, dd, J = 1.6 and 8 Hz), 8.72 (1H, dd, J = 0.8 and 8.4 Hz), 12.25 (1H, s), 13.60 – 13.90 (1H, br s).

Example 9: δ_H (400MHz, DMSO-d6) 3.65 (3H, s), 4.81 (2H, s), 7.18 - 7.23 (3H, m), 7.58 – 7.65 (2H, m), 7.74 (2H, m), 7.89 – 7.93 (2H, m), 8.04 (1H, dd, J = 1.6 and 8 Hz), 8.15 – 8.16 (1H, m), 8.72 (1H, dd, J = 0.8 and 8.4 Hz), 12.24 (1H, s), 13.50 – 14.00 (1H, br s).

B. Example compounds synthesised using Method A, scheme (aa)

Example 10: 2-[2-(Biphenyl-4-yloxy)-ethanoylamino]-benzoic acid

a) 2-[2-(Biphenyl-4-yloxy)-ethanoylamino]-benzoic acid methyl ester

Methyl (2-chloroacetyl)anthranilate (0.5 g, 2.2 mmole, 1 equiv), 4-phenylphenol (0.45 g, 2.64 mmole, 1.2 equiv) and potassium carbonate (0.456 g, 3.3 mmole, 1.5 equiv) were heated to 90°C in DMF (10 ml) for 6 hours. The solvent was removed by evaporation and the residue was chromatographed over a column of silica 60 eluting with DCM to give the title compound as a white solid (460 mg, 58%); δ_H (400MHz, DMSO-d6) 3.91 (3H, s), 4.80 (2H, s), 7.20 (2H, d, J = 8.8 Hz), 7.22-7.27 (1H, m), 7.30 – 7.36 (1H, m), 7.44 (2H, t, J = 8.0 Hz), 7. 60 – 7.70 (5H, m), 8.02 (1H, dd, J = 1.2 and 8 Hz), 8.64 (1H, d, J = 8 Hz); m/z 362.1 [MH^+], 384.1 [MNa^+].

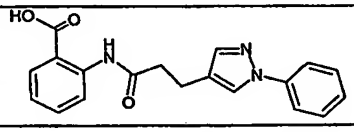
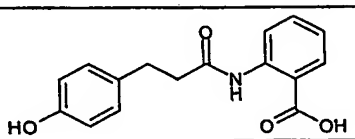
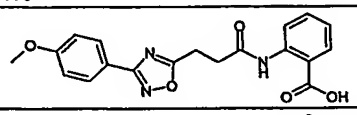
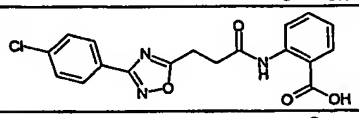
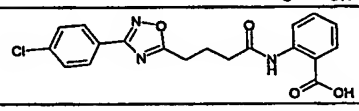
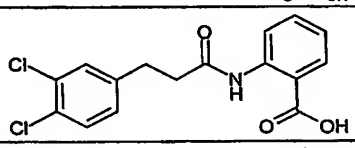
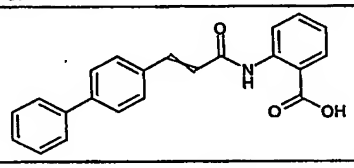
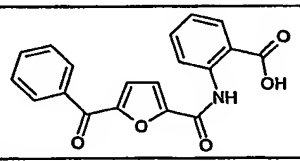
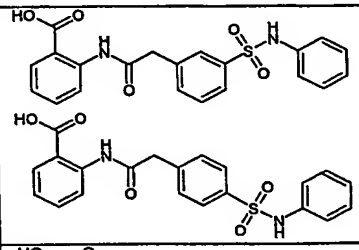
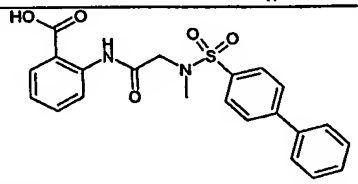
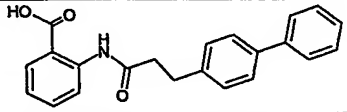
b) 2-[2-(Biphenyl-4-yloxy)-ethanoylamino]-benzoic acid

Methyl (4-phenylphenoxy)acetylanthranilate (153 mg, 0.42 mmole, 1 equiv) was dissolved in a mixture of water and ethanol (2 : 1, 10 ml) and the solution was heated to reflux with 2M NaOH solution (0.23 ml, 0.46 mmole, 1.1 equiv) overnight. The product was twice extracted from the cooled reaction mixture with ethyl acetate and the combined extracts were evaporated to give a crude product (146 mg) which was chromatographed over silica 60 eluting with DCM / MeOH (10 : 1) to give the title compound (35 mg, 24%); δ_H (400MHz, DMSO-d6 / D_2O) 4.74 (2H, s), 7.16 (1H, t, J = 7.8 Hz), 7.20 (2H, d, J = 8.7 Hz), 7.33 (1H, t, J = 7.3 Hz), 7.45 (2H, t, J = 7.8 Hz), 7. 52 (1H, dd, J = 1.4 and 8.5 Hz), 7.63 (4H, t, J = 8.3 Hz), 8.05 (1H, d, J = 6.9 Hz), 8.61 (1H, d, J = 8.2 Hz); m/z 348.1 [MH^+], 370.1 [MNa^+].

Example 11: 2-[2-(3-Bromo-phenoxy)-ethanoyl amino]-benzoic acid

δ_H (400MHz, DMSO-d6) 4.78 (2H, s), 7.12 (1H, dd), 7.18 - 7.22 (2H, m), 7.30 – 7.34 (2H, m), 7.65 (1H, t), 8.03 (1H, d), 8.71 (1H, d), 12.17 (1H, d), m/z

C. Example compounds synthesised using Method B

Example	Structure	LCMS [M-H$^+$]
12		334.04
13		283.94
14		365.97
15		370.20
16		383.41
17		337.91
18		343.88
19		334.28
20*		409.44
21		426.00[M+H$^+$]
22		344.41

* Acetic acids purchased as a mixture of isomers

Propionic acids for preparation of examples 12-22 are commercially available or known compounds.

Selected NMR data:

Example 12:
δ_H (400MHz, DMSO-d6) 2.74 (2H, t), 2.84 (2H, t), 7.14(1H, t), 7.27 (1H, t), 7.46 (2H,t), 7.58 (1H, t), 7.63 (1H, s), 7.75 (2H, d), 7.96 (1H, d), 8.33 (1H, s), 8.50 (1H, d), 11.16 (1H, br.s), 13.30 (1H, br.s); m/z 334.04 [M-H$^+$].

Example 13:
δ_H (400MHz, MeOH) 2.65 (2H, t), 2.92 (2H, t), 6.68 (2H, d), 7.05 (2H, d), 7.12 (1H, br.s), 7.51 (1H, t), 8.06 (1H, br.s), 8.54 (1H, d);
m/z 283.97 [M-H$^+$].

Example 14:
δ_H (400MHz, DMSO-d6) 3.03 (2H, t), 3.27 (2H, t), 3.83 (3H, s), 7.08 (2H, d), 7.14 (1H, t), 7.56 (1H, t), 7.92 (2H, d), 7.98 (1H, d), 8.41 (1H, d), 11.30 (1H, br.s), 13.55 (1H, br.s); m/z 365.97 [M-H$^+$].

Example 15:
δ_H (400MHz, DMSO-d6) 3.05 (2H, t), 3.31 (2H, t), 7.13 (1H, t), 7.57 (1H, t), 7.63 (2H, d), 7.98 (3H, m), 8.40 (1H, d), 11.30 (1H, br.s), 13.55 (1H, br.s); m/z 370.20 [M-H$^+$].

Example 16:
δ_H (400MHz, DMSO-d6) 2.14 (2H, m), 2.58 (2H, t), 3.10 (2H, t), 7.11 (1H, t), 7.55 (1H, t), 7.63 (2H, d), 7.95 (1H, d), 7.98 (2H, d), 8.43 (1H, d), 11.15 (1H, br.s), 13.40 (1H, br.s); m/z 383.41 [M-H$^+$].

Example 17:
δ_H (400MHz, DMSO-d6) 2.75 (2H, t), 2.94 (2H, t), 7.13 (1H, t), 7.29 (1H, d), 7.52 (1H, d), 7.56 (2H, m), 7.96 (1H, d), 8.44 (1H, d), 11.11 (1H, br.s), 13.35 (1H, br.s); m/z 337.91 [M-H$^+$].

Example 18:
δ_H (400MHz, DMSO-d6) 6.92 (1H, d), 7.18 (1H, t), 7.40 (1H, t), 7.50 (2H, t), 7.62 (1H, t), 7.68 (1H, d), 7.74 (4H, m), 7.83 (2H, m), 8.03 (1H, d), 8.60 (1H, d), 11.45 (1H, br.s); m/z 343.88 [M-H$^+$].

Example 21:

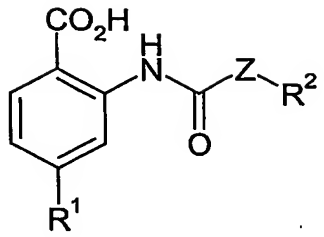
δ_H (400MHz, DMSO-d6) 2.90 (3H, s), 3.90 (2H, s), 7.19 (1H, t), 7.45 (1H, m), 7.51 (2H, t), 7.60 (1H, t), 7.75 (2H, d), 7.93 (4H, s), 8.02 (1H, d), 8.59 (1H, d), 12.00 (1H, br.s); m/z 425.00 $[M+H^+]$.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

Claims

1. A compound of Formula (I)



(I)

and salts, solvates and physiologically functional derivatives thereof, wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, or heterocyclic or alicyclic ring;

Z represents $-(CH_2)_n-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_nO-$; $-C(R^4R^5)O-$ or -Y-W-X- ;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 or 2;

q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

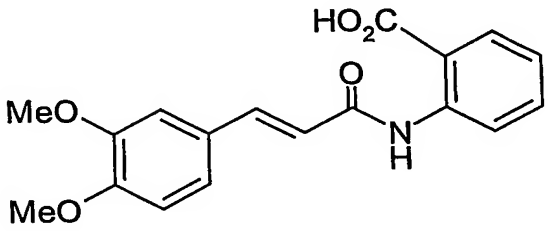
R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl;

provided

(i) that when R^1 is hydrogen, Z is $-(CH_2)_n-$, and n is 2, then R^2 is other than para-chlorophenyl or para-methylphenyl and

(ii) that a compound of Formula (I) is is other than 2-(2-(((4-(phenyl)phenyl) amino)acetyl)amino)benzoic acid, 2-(2-(((4-phenyl)phenoxy)acetyl)amino) benzoic acid, 2-[[(4-cyclohexylphenoxy)acetyl]amino]benzoic acid, 2-[[3-[3-(4-

chlorophenyl)-1,2,4-oxadiazol-5-yl]-1-oxopropyl]amino]benzoic acid or compound X



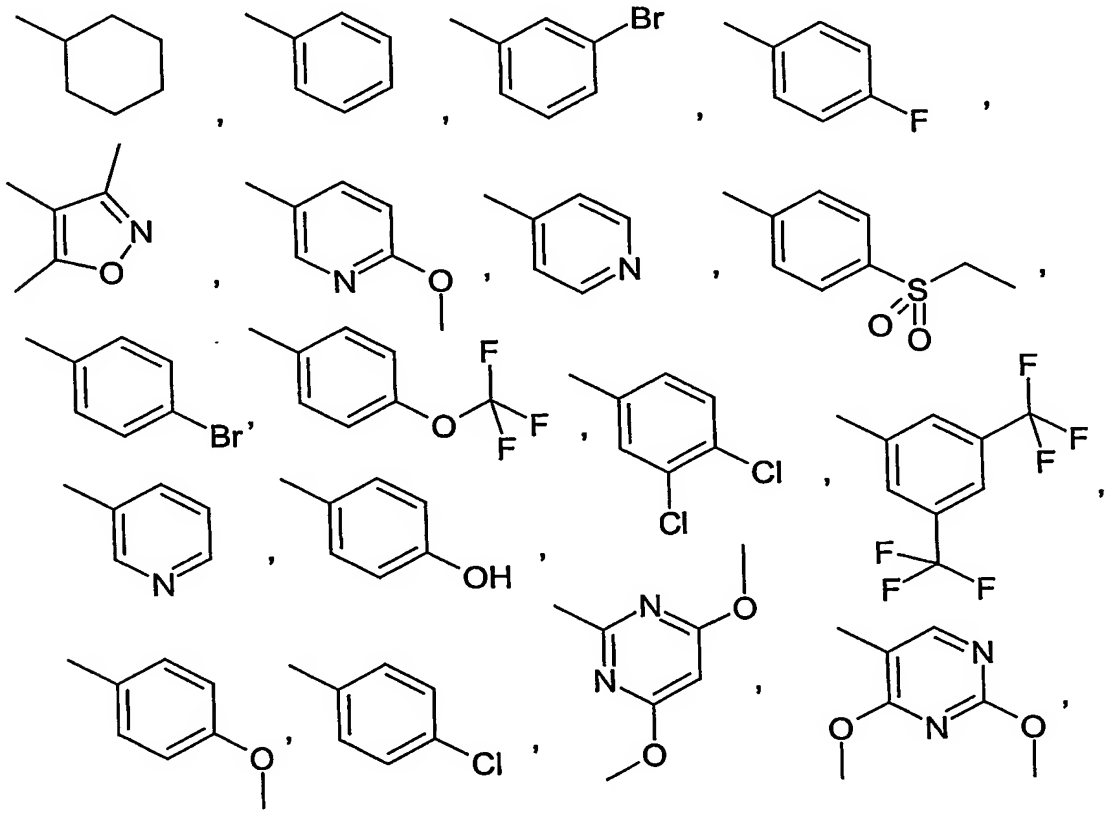
X.

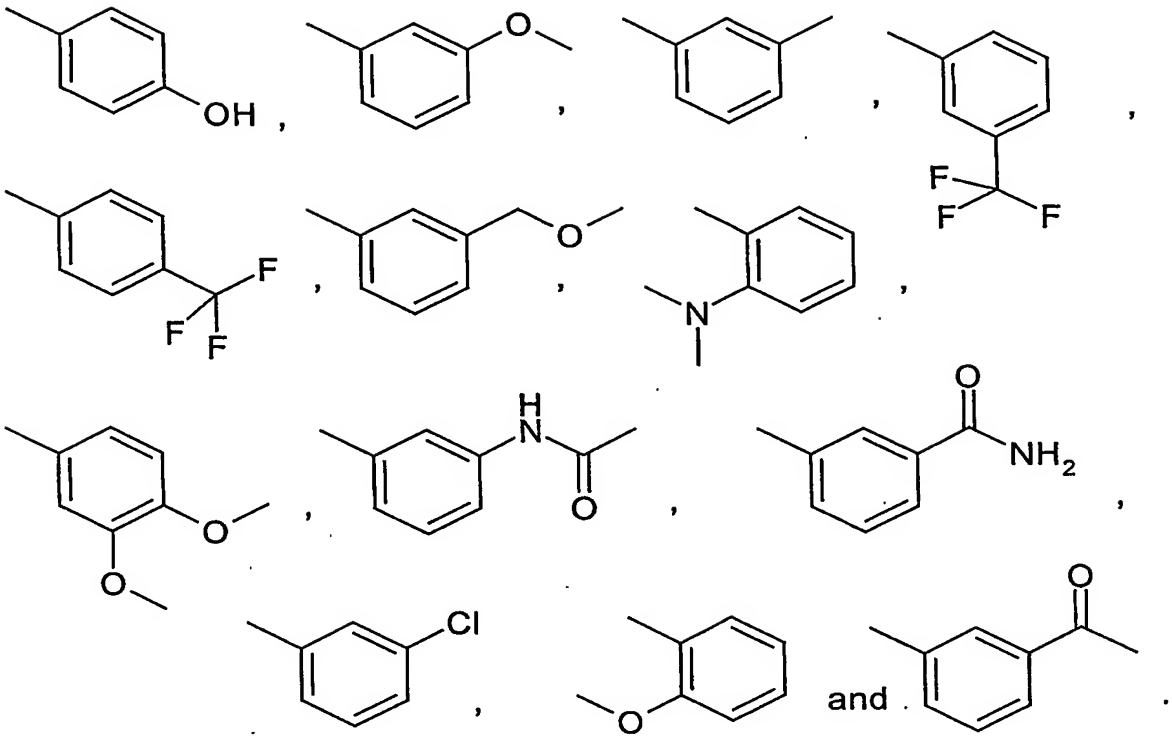
2. A compound according to claim 1 wherein R^1 is hydrogen or methyl.

3. A compound according to claim 2 wherein R^1 is hydrogen.

4. A compound according to any preceding claim wherein R^2 is cyclohexyl, phenyl, pyridine, pyrimidine, pyridazine or isoxazole.

5. A compound according to any one of claims 1-3 wherein R^2 is selected from the group consisting of:





6. A compound according to any one of claims 1-3 wherein R^2 is substituted phenyl.

7. A compound according to claim 6 wherein R^2 is phenyl substituted with one or two substituents selected from halogen C_{1-3}alkyl, C_{1-3}haloalkyl C_{1-3}alkoxy and C_{1-3}haloakloxy.

8. A compound according to any preceding claim wherein Y is –O— or $-CH_2-$.

9. A compound according to any preceding claim wherein X is absent or is $-SO_2NR^3-$, –NHC(O)– or –NHC(O)NH– .

10. A compound according to any preceding claim wherein Y is $-CH_2-$ and X is $-SO_2NR^3-$.

11. A compound according to any one of claims 1- 7 wherein Y is –O– and X is absent.

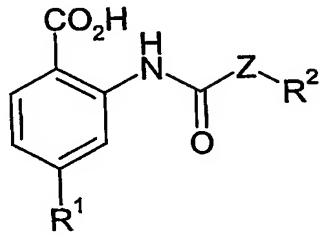
12. A compound according to any preceding claim wherein W is a 5 or 6 member aryl or heteroaryl ring.

13. A compound according to claim 12 wherein W is phenyl.

14. A compound according to claim 12 wherein W is a 5 member heteroaryl ring.

15. A compound according to any preceding claim for use in human or veterinary medicine

16. A compound of Formula (Ia)



(Ia)

and salts, solvates and physiologically functional derivatives thereof, for use in the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia or of inflammatory diseases or conditions

wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, or heterocyclic or alicyclic ring;

Z represents $-(CH_2)_n-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_qO-$; $-C(R^4R^5)O-$ or $-Y-W-X-$;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 or 2;

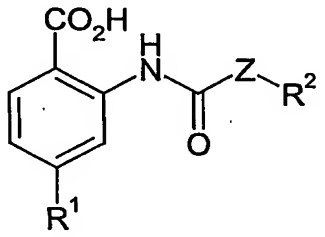
q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl.

17. A compound according to claim 16 wherein the use is in the treatment of diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease or stroke.

18. Use of a compound of Formula (Ia)



(Ia)

and salts, solvates and physiologically functional derivatives thereof in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia or of inflammatory diseases or conditions

wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, or heterocyclic or alicyclic ring;

Z represents $-(CH_2)_n-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_qO-$; $-C(R^4R^5)O-$ or $-Y-W-X-$;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

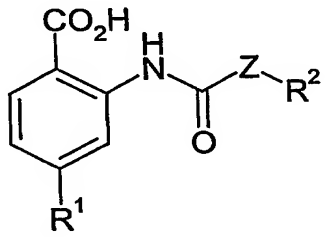
p represents an integer selected from 0, 1 or 2;

q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl.

19. A method for the treatment of a human or animal subject having disease characterised by under-activation of the HM74A receptor or in which activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of a compound of Formula (Ia)



(Ia)

and salts, solvates and physiologically functional derivatives thereof wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, or heterocyclic or alicyclic ring;

Z represents $-(CH_2)_n-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_qO-$; $-C(R^4R^5)O-$ or $-Y-W-X-$;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 or 2;

q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl.

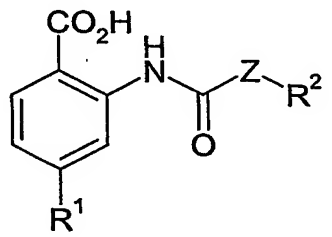
20. A method according to claim 19 wherein the condition is a disorder of lipid metabolism including dislipidaemia or hyperlipoproteinaemia or an inflammatory disease or condition.

21. A pharmaceutical formulation comprising a compound according to any one of claims 1-14 in admixture with one or more physiologically acceptable diluents, excipients or carriers.

22. A combination for administration together or separately, sequentially or simultaneously in separate or combined pharmaceutical formulations, said combination comprising a compound according to any one of claims 1-14 together with another therapeutically active agent.

23. A pharmaceutical formulation comprising a compound according to any one of claims 1-14, plus a further active ingredient selected from the group consisting of statins, fibrates, bile-acid binding resins and nicotinic acid and one or more physiologically acceptable diluents, excipients or carriers.

24. A method for the preparation of a compound of Formula (I)



(I)

in which R^1 represents hydrogen, Z represents -Y-W-X-, Y represents $-(CH_2)_pO-$, p represents the integer 1, and W, X and R^2 are as defined in claim 1, the method comprising the steps of:

(i) amide bond formation by acetylation of an ester of anthranilic acid;

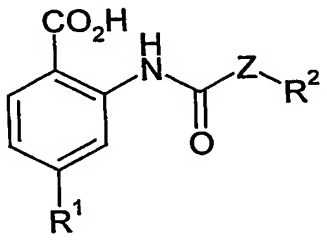
(ii) addition of W or W-X-R^2 by sustitution of G;

(iii) deprotection of the anthranilic acid group;

and where desired or necessary converting a resultant free acid or base compound of Formula (I) into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.

25. A method according to claim 24 where in step (ii) comprises addition of W and a further step (ii)(a), addition of R^2, is included in the form of a further substitution reaction.

26. A method for the preparation of a compound of Formula (I)



(I)

the method comprising the steps of:

(i) formation of an amide between the amine group of 2-amino-bezoic acid and an activated acyl transfer reagent derived from a carboxylic acid

(ii) where desired or necessary converting a resultant free acid or base compound of Formula (I) into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.